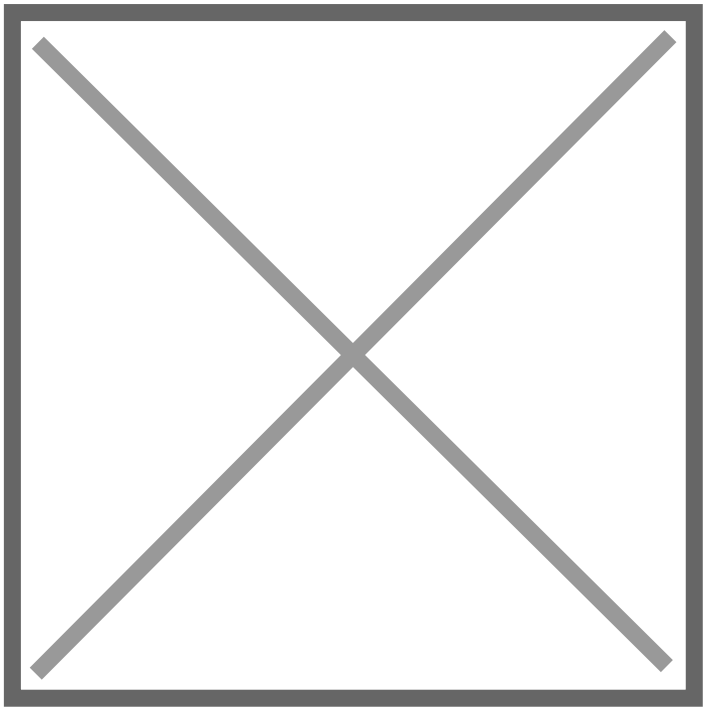
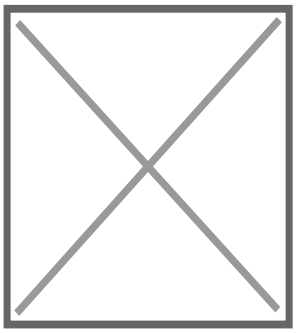
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Quality by Design for manufacturing of biopharmaceuticals

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Quality by Design (QbD) has gained great popularity in the last five years. Intended to be an initiative to modernize pharmaceutical manufacturing and make it more efficient, the elements of QbD have been presented in the FDA's PAT-A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance1 as well as the International Conference on Harmonization (ICH) guidelines: ICH Q8 Pharmaceutical Development2, ICH Q9 Quality Risk Management3 and ICH Q10 Pharmaceutical Quality System4.

In the traditional approach to biotech production, manufacturers would define a process and run it consistently such that the critical parameters are controlled within a narrow range so as to make the product with consistent quality. The major downside of this approach is that since the process controls are fixed, variability in raw materials and process manifests as variability in product quality and results in lot failures5. In contrast, Quality by Design is defined in the ICH Q8 guideline as Ã¢â?¬Å?a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.Ã¢â?¬?2. Figure 1 (on page 59) illustrates the roadmap for QbD implementation and shows the key steps that need to be taken for implementing QbD for a biotech product5-7. Key steps are: identification of the product attributes that are of significant importance to the product's safety and/or efficacy (Target Product Profile and Critical Quality Attributes); design of the process to deliver these attributes; a robust control strategy to ensure consistent process performance; validation and filing of the process demonstrating the effectiveness of the control strategy; and finally ongoing monitoring to ensure robust process performance over the life cycle of the product. Furthermore, risk assessment and management, raw material management, use of statistical approaches and process analytical technology (PAT) provides a foundation to these activities.

Figure 2 (on page 59) shows a case study that illustrates application of QbD for a Pichia pastoris expressed biotech product8. First, Failure Modes and Effects Analysis (FMEA) was performed to identify process parameters for process characterization. Risk Priority Number (RPN) scores were calculated and operating parameters with a high enough RPN score were characterized using a qualified scaled-down model. Screening was first performed to identify the process parameters that had the most impact on % solids, optical density (OD) profiles and product titer. 12 parameters were examined in the screening study and based on the results of the screening study, three parameters were further examined for their interactions. The parameters were temperature, pH, and dissolved oxygen (DO).

A design of experiments (DOE) study was designed to examine the main effect of these parameters on % solids, OD profiles and product titer along with their interactions. The outcome of the DOE is illustrated in Figure 3A for the effect on product titer. It was found that none of the parameters have significant impact on product quality (no critical parameters)8. Further, temperature, pH and DO were found to impact cell growth and titer, and thus were classified as key process parameters. As per the principles in the ICH Q8 guideline, a unit operation design space was established using the acceptable ranges for temperature, pH and DO and this is illustrated in Figure 3B8.

Another case study illustrating the benefits of QbD with respect to real time release is shown in Figure 49. In this application, near-infrared (NIR) analysis allows for trending of raw material lot quality in real time and early detection of any shifts in quality. The subsequent extrusion unit operation is monitored continuously in-line for temperature and active ingredient concentration. Off-line, an ultra-performance liquid chromatography test is performed to test the material for presence of a degradation product. Particle size distribution is continuously monitored during milling for process consistency and controlled via feedback control for compressing performance as a function of particle size. Finally, the weight, thickness, potency and hardness are tested at-line at the tablet press for continuous quality verification and feedback control of compression. This approach reduces quality risk and variability while increasing process understanding and a real time profile for the manufacturing process at each step or unit operation can be generated. If the reported profile is consistent with historical data, based on population analysis, real time release of product can be considered. Fundamentally, only those lots that fall outside the known population of data would require additional off-line testing or be rejected. Such an approach can result in very significant cost savings as well as an improved consistency in product quality.

Current environment of Indian biopharma industry

Historically, the Indian biotech companies have demonstrated their capability to manufacture biotech drugs safely and effectively. India is already the world's top vaccine manufacturer and is widely recognized as a potential leader for manufacturing of other human therapeutic biotech drugs9. Most of the drugs are those called as 'biosimilars', meaning copies of drugs that are already on the market10. However, the sales of such biosimilars manufactured in India have primarily been limited to developing and under developed countries. As the Indian biotech industry gears up for getting approvals for selling the biosimilars to the European, North American and other developed markets, it will be necessary for the manufacturers to raise their technical, quality and compliance systems to the expectations of the regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA). Implementation of Quality by Design is one such initiative that will assist in making this leap. The Indian biotech industry realizes this and most of the key players are embracing QbD by integrating its principles into their internal systems.

The future success of the Indian biotech industry will be significantly impacted by how quickly it adapts to the higher expectations of the regulatory authorities of the developed nations. Quality by Design is likely to play a key role in this transition.

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